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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/20/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/728,486	ECKER ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-29,31-35,37,38,50-60,62-71,73-78 and 80-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-29,31-35,37,38,50-60,62-71,73-78 and 80-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Interpretation

1. The amendment clarifies that "base composition" are based upon mass spectrometry and determine the nucleotide composition of the amplification product.

Claim Rejections - 35 USC § 102

2. The rejection of claims 27, 28, 32-34, 36-38, 50, 69, 70, 72-76, 79, 80, 81, 84 and 85 under 35 U.S.C. 102(b) as being anticipated by Hurst et al (Rapid Comm. Mass Spectrom. (1996) 10:377-382) is withdrawn in view of the amendment.

3. The rejection of claims 27-29, 31-35, 38, 50-60, 63-71, 74-78 and 81-87 under 35 U.S.C. 102(b) as being anticipated by Hoffman et al (Arch. Virol. (2001) 146:2275-2289) is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 27, 28, 32-34, 36-38, 50, 69, 70, 73-76, 80, 81, 84 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hurst et al (Rapid Comm. Mass Spectrom. (1996) 10:377-382) in view of either Muddiman et al (Anal. Chem. (1997) 69:1543-1549) or Chen (U.S. Patent 6,613,509).

Hurst teaches a method of claims 27, 69 and 75 of identifying a pathogenic bioagent in sample (see page 377, column 1), comprising:

(a) amplifying a plurality of segments of nucleic acid of said pathogen with a plurality of primer pairs to obtain a plurality of amplification products (see page 378, table I, and page 378, column 2, where PCR was performed using two sets of primer pairs, one directed to the 5S rRNA gene and one directed to the mip gene fragment)

(b) *determining the base compositions of at least two members of said plurality of amplification products wherein said base compositions identify said pathogen in said sample* (see page 379, figure 1, where Hurst performs MALDI-TOF on both PCR products to determine base composition as the mass of the PCR product, and shows that this is a feasible method of detecting Legionella).

With regard to claims 28, 70, 81, Hurst teaches detection of a bacterial pathogen (see page 379, figure 1, where Legionella is detected).

With regard to claims 32-34, 76, Hurst teaches the use of specific primers that are genus and species specific (see page 378, table 1).

With regard to claim 36, Hurst teaches the base compositions of both the mip and 5S rRNA pcr products (see page 379, figure 1).

With regard to claims 37, 72, 73, 79, 80, Hurst teaches the use of MALDI-TOF (see abstract).

With regard to claims 38, 74, 84, Hurst teaches analysis of the 5S rRNA gene using primers directed to that gene (see page 378, table 1).

With regard to claims 50, 85, Hurst teaches analysis of the mip gene, which encodes a protein involved in virulence (see page 378, table 1).

Hurst does not determine the base composition by identifying the numberr of individual nucleotides in the amplification product.

Muddiman teaches analysis of base composition of PCR products of microorganisms wherein the base compositions identify the number of each individual nucleotide present in the amplification products without seuqencing the amplification products and wherein the base compositions identify the organism in the sample (see abstract). Muddiman exemplifies the base composition analysis in Table 1, showing the base compositions for a variety of PCR products.

Chen also teaches analysis of base composition of PCR products of microorganisms wherein the base compositions identify the number of each individual nucleotide present in the amplification products without seuqencing the amplification

products and wherein the base compositions identify the organism in the sample (see claim 1, for example).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the Mass spectrometry base composition analysis methods of Muddiman or Chen in the mass spectrometry analysis method of Hurst since Hurst expressly teaches mass spectrometric analysis of PCR products and since Muddiman expressly teaches "In this work, we have demonstrated that the complementary nature of DNA due to Watson-Crick base-pairing provides constraints that can be exploited in conjunction with the measured mass to allow determination of the number of base pairs and the base composition for relatively large DNA fragments. This approach uses accurate mass measurements and can be extended by the use of mass shifts induced by modified base PCR or postamplification modification, providing a rapid and accurate scheme by which to characterize PCR products of increasing size. This scheme should be particularly attractive for rapid confirmation of the base composition of PCR products (see page 1549, column 2)." An ordinary practitioner would have been motivated to improve the Hurst method by the use of the base composition analysis method of Muddiman in order to rapidly and accurately characterize the PCR products of Hurst down to the base composition level in order to confirm what sequence is present in the sample.

. Further and distinct motivation to determine the base composition is provided by Chen, who notes "Using this technique, base compositions of DNA fragments have

been determined with an accuracy of .+-.0.03% with respect to their known sequences. The comparisons of base compositions among homologous sequences are useful in sequence validation, sequence comparison, and characterizations of sequence polymorphisms. In particular, the efficiency and accuracy of MALDI-TOF MS which provides analysis of molecular masses of short DNA molecules within seconds are employed to obtain the base composition of a polymerase chain reaction (PCR) product solely from its molecular weight (see column 4, lines 45-56)." An ordinary practitioner would have been motivated to use the Chen method to determine the base composition in order to permit sequence comparisons in an efficient and accurate way using the mass spectrometric method of Hurst combined with the mass spectrometric and analysis methods of Chen.

Therefore, an ordinary practitioner, motivated to detect pathogens by Hurst, would have been motivated by both Muddiman and Chen to perform base composition analysis in order to obtain the benefits of increased speed, accuracy without the requirement to use gel electrophoresis or other sequencing methods.

6. Claims 27-29, 31-35, 37, 38, 50-60, 62-71, 73-78 and 80-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffman et al (Arch. Virol. (2001) 146:2275-2289) in view of Koster (WO 98/20166) and further in view of either Muddiman et al (Anal. Chem. (1997) 69:1543-1549) or Chen (U.S. Patent 6,613,509).

Hoffman teaches a method of claims 27, 53, 69 and 75 of identifying a pathogenic bioagent in sample (see page 2278, where influenza is the bioagent), comprising:

(a) amplifying a plurality of segments of nucleic acid of said pathogen with a plurality of primer pairs to obtain a plurality of amplification products (see page 2278, subheading "Design of oligonucleotides for RT-PCR" and pages 2278-2281, which detail a PCR reaction that was performed using eight sets of primer pairs, directed to the eight segments of the influenza virus)

(b) *determining the base compositions of at least two members of said plurality of amplification products wherein said base compositions identify said pathogen in said sample* (see page 2281, figure 3, where the base composition in terms of mass is determined by gel electrophoresis).

With regard to claims 28, 54, 70, 81, Hoffman teaches detection of a viral pathogen (see page 2281, figure 3, where Influenza virus is detected).

With regard to claims 29, 55, 71, 82, Hoffman teaches the use of tissue sample (see page 2277, where tissue from embryonated eggs is used and see page 2276, where virus isolation occurs from the throat of mammals).

With regard to claim 31, 56, 57, 83, Hoffman teaches that samples can be obtained from mammals and teaches the virus infects humans (see page 2276).

With regard to claims 32-34, 58-59, 76, Hoffman teaches the use of specific primers that are viral genus specific (see page 2278).

With regard to claim 35, 60, 77, 78, Hoffman teaches detection of viral subtypes using the primers (see figure 4, page 2282 and figure 5, page 2283 (and table 3) where primers specific for each subtype were used).

With regard to claims 38, 63, 74, 84, Hoffman teaches analysis of all of the genes of Influenza A, including any housekeeping genes (see page 2281, figure 2, where all of the eight segments of Influenza A are amplified).

With regard to claims 50, 51, 64, 65, 85, 86, Hoffman teaches analysis of all of the influenza A virus genes, including genes involved in virulence and the Influenza polymerase genes, PB1, PB2 and PA which form a heterotrimer (see page 2281, figure 2).

With regard to claim 66, 68, Hoffman teaches the use of eight primer pairs (see page 2281, figure 2).

With regard to claim 52, 67, 87, Hoffman teaches analysis "In pandemic situations where a new virus subtype emerges, we could either use the plasmid collection already available or quickly generate plasmids iwth the same or similar sequences, and use it to develop antiviral therapies (i.e., vaccines). Thus, a universal primer set is a powerful tool that can be used in classic and reverse genetics methods to prevent and contain future influenza A epidemics and pandemics (see page 2287)."

Hoffman teaches PCR to analyze and compare the viral subtypes but does not teach mass spectrometry or base composition signatures.

Koster teaches a method for detecting a single nucleotide polymorphism in an individual using molecular mass measurements such as MALDI TOF (page 14, for example), by determining the molecular mass of said amplification product using mass spectroscopy (page 13, line 1 and page 157, lines 10-29 and example 19) and comparing the molecular mass to the molecular mass of said region in an individual known to have said polymorphism, where if said molecular masses are the same then said individual has said polymorphism (page 13, lines 2-5 and page 158, lines 1-29, where Koster expressly compares patient 1 to a negative control and example 19).

With regard to claims 36, 37, 61, 62, 72, 73, 79 and 80, Koster expressly teaches comparison of base compositions with both modified and unmodified products wherein the base compositions identify the number of each individual nucleotide present in the amplification products without seuqencing the amplification products and wherein the base compositions identify the organism in the sample (see page 66, for example, as well as page 105, table II and pages 69-70). At page 105, table II, Koster provides the base composition of three different PCR products determined by MALDI-TOF. Further, Koster specifically discusses using base composition to analyze mutations as discussed on page 70, where Koster notes "MS can also be used to determined full or partial sequences of larger DNAs; this can be used to detect, locate, and identify new mutations in a given gene region."

In particular, Koster expressly teaches the use of MALDI-TOF for diagnosis of bacterial or viral infections (see pages 73-79). Koster exemplifies this analysis in

Example 5.

Muddiman teaches analysis of base composition of PCR products of microorganisms wherein the base compositions identify the number of each individual nucleotide present in the amplification products without seuqencing the amplification products and wherein the base compositions identify the organism in the sample (see abstract). Muddiman exemplifies the base composition analysis in Table 1, showing the base compositions for a variety of PCR products.

Chen also teaches analysis of base composition of PCR products of microorganisms wherein the base compositions identify the number of each individual nucleotide present in the amplification products without seuqencing the amplification products and wherein the base compositions identify the organism in the sample (see claim 1, for example).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the Mass spectrometry and base composition analysis method of Koster in the analytical method of Hoffman since Koster states "In another embodiment, an accurate sequence determination of a relatively large target nucleic acid, can be obtained by generating specifically terminated fragments from the target nucleic acid, determining the mass of each fragment by mass spectrometry and ordering the fragments to determine the sequence of the larger target nucleic acid (see

page 75, line 26 to page 76, line 2)." So an ordinary practitioner would have been motivated to detect the PCR products of Muddiman with the base composition Mass spectrometric approach of Koster since Koster teaches that Mass Spectrometry is accurate and can improve the speed, mass accuracy and precision of the analysis (see abstract, for example).

Further, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the Mass spectrometry base composition analysis methods of Muddiman or Chen in the mass spectrometry analysis method of Hoffman since Muddiman expressly teaches "In this work, we have demonstrated that the complementary nature of DNA due to Watson-Crick base-pairing provides constraints that can be exploited in conjunction with the measured mass to allow determination of the number of base pairs and the base composition for relatively large DNA fragments. This approach uses accurate mass measurements and can be extended by the use of mass shifts induced by modified base PCR or postamplification modification, providing a rapid and accurate scheme by which to characterize PCR products of increasing size. This scheme should be particularly attractive for rapid confirmation of the base composition of PCR products (see page 1549, column 2)." An ordinary practitioner would have been motivated to improve the Hoffman method by the use of the base composition analysis method of Muddiman in order to rapidly and accurately characterize the PCR products of Hoffman down to the base composition level in order to confirm what sequence is present in the sample.

Further and distinct motivation to determine the base composition is provided by Chen, who notes "Using this technique, base compositions of DNA fragments have been determined with an accuracy of .+-.0.03% with respect to their known sequences. The comparisons of base compositions among homologous sequences are useful in sequence validation, sequence comparison, and characterizations of sequence polymorphisms. In particular, the efficiency and accuracy of MALDI-TOF MS which provides analysis of molecular masses of short DNA molecules within seconds are employed to obtain the base composition of a polymerase chain reaction (PCR) product solely from its molecular weight (see column 4, lines 45-56)." An ordinary practitioner would have been motivated to use the Chen method to determine the base composition in order to permit sequence comparisons in an efficient and accurate way using the PCR method of Hoffman combined with the mass spectrometric and analysis methods of Chen for analysis of PCR products.

Therefore, an ordinary practitioner, motivated to detect pathogens by Hoffman, would have been motivated by all of Koster, Muddiman and Chen to perform base composition analysis in order to obtain the benefits of increased speed, accuracy without the requirement to use gel electrophoresis or other sequencing methods.

Double Patenting

7. Claims 27-29, 31-35, 37, 38, 50-60, 62-71, 73-78 and 80-87 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 7,108,974. Although the conflicting claims are not

identical, they are not patentably distinct from each other because the copending application claims represent a species of the current claims in which specific numbers of species are in the database and where specific mass is determined. Therefore, the species of claims 59,60,62,63,66,69-76 and 79-94 of copending Application No. 10/156,608 anticipates the current, more generic claims and renders them prima facie obvious.

8. Claims 27-29, 31-35, 37, 38, 50-60, 62-71, 73-78 and 80-87 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-19 and 29-38 of copending Application No. 10/660,997. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application claims represent a species of the current claims in which specific numbers of species are in the database and where specific mass is determined. Therefore, the species of claims 14-19 and 29-38 of copending Application No. 10/660,997 anticipates the current, more generic claims and renders them prima facie obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. Claims 27-29, 31-35, 37, 38, 50-60, 62-71, 73-78 and 80-87 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10, 14, 17, 28-44 of copending Application No. 10/660,996. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application claims represent a species

of the current claims in which specific numbers of species are in the database and where specific mass is determined. Therefore, the species of claims 1-10, 14, 17, 28-44 of copending Application No. 10/660,996 anticipates the current, more generic claims and renders them prima facie obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. Claims 27-29, 31-35, 37, 38, 50-60, 62-71, 73-78 and 80-87 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 23-27, 30-34, 44-55 of copending Application No. 10/660,122. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application claims represent a species of the current claims in which specific numbers of species are in the database and where specific mass is determined. Therefore, the species of claims 23-27, 30-34, 44-55 of copending Application No. 10/660,122 anticipates the current, more generic claims and renders them prima facie obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Response to Arguments

12. Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

The only argument that remains at all relevant is the argument that Hoffman in view of Koster do not teach base composition analysis. While this argument is not persuasive, the addition of Muddiman and Chen necessitated by the amendment serve clarify that the state of the prior art clearly teaches base composition analysis and that Koster clearly teaches this element. Specific motivation is provided in the rejections.

Applicant refers to an accompanying declaration, but no declaration was filed.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
12/13/06